ORIGINAL RESEARCH

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Benefits of Neoadjuvant Chemotherapy for Luminal Breast Cancer with Respect to Tumor Response

Bala Başak ÖVEN[a], Serkan ÇELİK[a], Günay GÜRLEYİK[b], Fügen AKER VARDAR[c], Ezgi YÜZÜGÜLLÜ ÇOBAN[d], Mesut ŞEKER[d], İlker Nihat ÖKTEN[e], Ali AKTEKIN[f]

[a]Department of Medical Oncology, Bahçeşehir University Medical Faculty, İstanbul, TURKEY
[b]Department of General Surgery, Haydarpasa Numune Educartion and Research Hospital, İstanbul, TURKEY
[c]Department of Pathology, Haydarpasa Numune Educartion and Research Hospital, İstanbul, TURKEY
[d]Department of Medical Oncology, Bezmi Alem University, Medical Faculty, İstabul,TURKEY
[e]Department of General Surgey Gaziantep University, Medical Faculty, Gaziantep, TURKEY

ABSTRACT Objective: The pathological complete response (PCR) rate following neoadjuvant chemotherapy (NAC) is prognostic for overall survival (OS). We evaluated the pathological responses to NAC and related factors in luminal type HER2-positive breast cancer. **Materials and Methods:** Hormone receptor (H), HER2/neu status, and Ki67 index were evaluated on 258 core biopsies of breast cancer before NAC. In total, 194 cancer core biopsies were found to be luminal A or B. A Ki67 index of above 20% together with hormone receptor positivity and HER2 negativity further confirmed the breast cancer type as luminal B. The relation between pathological responses and the data obtained were evaluated using the Chi-square test. The OS and disease-free survival (DFS) and related factors were analyzed with univariate analysis. **Results:** PCR was achieved in 47 (18.2%) patients, and the objective response was 70.2% after NAC. The 5-year DFS rate was 59.2% that related to surgery type; T, N, and postoperative stages; lymphovascular invasion (LVI); perineural invasion (PNI); and pathological response to NAC ($p<0.001$). The median OS could not be reached, and the 5-year OS rate was 88.5%. Furthermore, the N and postoperative stages, recurrence, and pathological response to NAC were related to OS. The hormone receptor positivity was related to pathological response ($p=0.03$). Although partial and complete responses were high among hormone receptor-negative tumors, the stable response was more common among hormone receptor-positive ones. **Conclusions:** It should be better to recommend NAC to hormone receptor-negative or HER2-positive tumors unless surgery could not be performed because of the locally advanced tumor due to lower rate of PCR or partial response with NAC in hormone receptor-positive tumors.

Keywords: Breast cancer; neoadjuvant chemotherapy; luminal type

Neoadjuvant chemotherapy (NAC) is one of the treatment options for patients with locally advanced breast cancer (LABC). Moreover, it is also used in early-stage breast cancer to shrink the primary tumor and facilitate breast-conserving surgery.[1] The clinical efficacy of NAC depends on the pathological tumor response detected after the surgery. Pathological complete response (PCR), defined as the disappearance of the invasive tumor both in the breast and axilla after NAC, is the target endpoint for the prognosis of breast cancer.[1] The shrinking of the axillary tumor is together with moving away from axillary dissection to candidate of sentinel lymph node biopsy.[1]

Several trials have reported survival-related PCR of 3 to 46% following NAC.[2] Immunohistochemical markers, estrogen receptor (ER) and progesterone receptor (PR) status, and HER2 expression, which determine the breast tumor subtypes could predict the response to NAC.[3,4] The rate of PCR was low among low-grade, hormone receptor (H)-positive tumors.[5] The NSABP study showed that ER-negative patients had a better response to NAC than ER-positive patients.[6] Similarly, the GEPARTRIO study reported PCR rates of 41% in triple-negative patients, 29% in H-negative patients, and 8% in H-positive ones.[7] These studies indicate that negative H status is a strong predictor of the response to NAC. Furthermore, PCR was associated with better DFS.[5] In contrast, PCR was not prognostic in patients with H-positive tumors in a pooled analysis conducted in Germany.[8]

Correspondence: Bala Başak ÖVEN
Department of Medical Oncology, Bahçeşehir University Medical Faculty, İstanbul, TURKEY/TÜRKİYE
E-mail: basakoven@yahoo.com

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The treatment plan for oncology patients in several oncology centers in Istanbul is decided by a multidisciplinary tumor board before the surgery, and NAC is being used with increasing frequency. Multiple patients with breast cancer have been directed for NAC independently from the molecular classification of their tumors by immunohistochemical analysis. Because of the concerns of chemotherapy toxicity and minimal response, not all patients with LABC are offered NAC. This study compared the response to NAC among breast cancer subtypes, especially for luminal tumors without HER2 expression among the Turkish population, and whether NAC was necessary. Furthermore, the significance of pathological response after NAC with respect to survival was studied.

MATERIALS AND METHODS

This study was conducted on 258 patients with breast cancer who were treated with NAC in the Oncology Department of three different centers in Istanbul from 2007 to 2018. Patients were stratified according to age, menopausal status, type of surgery, response to the treatment, histopathological properties, pathological response, and survival. The median age was 47 (24-94) years at the time of diagnosis. All patients were diagnosed by Tru-Core biopsy. Patients who were diagnosed by fine-needle aspiration biopsy or those without pathological specimens were excluded.

The patients were clinically staged before the surgery; five of them initially had metastatic disease, 168 patients had locally advanced cancer with clinically palpable fixed axillary lymph nodes, and other 57 patients had early-stage disease. While 66 patients underwent breast conservation surgery (BCS), modified radical mastectomy (MRM) was performed in 182 patients, and simple mastectomy without axillary dissection was performed in ten patients. All patients were staged according to the AJCC sixth edition of the cancer staging manual.[9] Although four patients had stage 4 disease because of single bone metastasis, they were not excluded and treated with curative intent.

Histopathological features were assessed using paraffin-embedded tissue and stained with hematoxylin and eosin. Next, H and HER2/neu status were determined immunohistochemically. Hormone receptor positivity was defined as positive above 1% cut-off value for both ER and PR. The pathologist scored HER2 by immunohistochemistry (IHC) staining as 0, 1+, 2++, or 3+ based on the intensity and proportion of membrane staining according to the criteria based on ASCO/CAP.[10] The histological type of the tumor, the size of the invasive component, the grade of the tumor, and the rate of lymph node involvement were recorded. PCR was defined as no residual invasive tumor in the breast or axillary lymph node after the surgery, irrespective of the presence of ductal carcinoma in situ. The sum of partial and complete responses was defined as the objective response rate. Following the surgery, if not completed preoperatively, adjuvant chemotherapy and radiotherapy were administered sequentially, if indicated. In addition, patients with positive H status and HER2 overexpression received adjuvant hormone therapy and trastuzumab therapy, respectively. Patients were followed up, and recurrences were recorded. The clinicopathological factors related to the pathological response after NAC were analyzed. In addition, the significance of these factors with respect to OS and DFS was analyzed.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive analysis was used to examine the distribution of study-level variables. The relationship between response to NAC and other clinicopathological factors was analyzed using the Chi-square test. The logistic regression analysis was performed to evaluate critical factors associated with treatment response. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. DFS was defined as the time from the surgery to the last follow-up, and the time until a relapse was defined as the time since surgery to the first evidence of relapse. In addition, OS was described as the time from the diagnosis to the date of the patient's death or last known contact. Univariate analysis of prognostic factors associated with the survival was performed using the Cox proportional hazards model. All p-values were two-sided in tests, and those less than or equal to 0.05 were considered significant.

RESULTS

The median age of patients was 47 years (range: 24-94 years), and 62% were premenopausal, whereas the remaining 38 were postmenopausal. Tumors were localized in the right breast in 108 patients (41.9%) and in the left breast in 145 patients (56.2%). The tumor was bilateral in five patients (1.9%).

In the NAC group, PCR for both breast and axillary lymph node was achieved for 47 (18.2%) patients, whereas PCR for lymph node and breast were 41.1% and 22.%, respectively; 51.9% of patients had partial responses. PCR was 31% in H-negative patients, higher than that in H-positive patients (13.9%). Although PD was observed in eight patients (8.1%), 69 patients had stable disease (26.7%). We could not find any factor related to the pathological response by logistic regression analysis other than the menopausal status (p=0.04), which was a significant predictor of the pathological response.

The most common chemotherapy regimens were anthracycline (doxorubicin-cyclophosphamide–taxane) and taxane received by 81% of patients. Sixty-five out of 96 HER2-positive patients received trastuzumab as a combination of NAC. Because dual-HER2 blockade was not approved during the study period, we could not use pertuzumab in addition to trastuzumab. Non-hematological toxicities were graded 1-2, and most common were alopecia and asthenia followed by nausea, arthromyalgia, and stomatitis, which occurred in fewer than 4% of patients. Only grade 3-4 hematological toxicity was neutropenia, observed in three patients. There was no need to reduce the dose because of myelotoxicity.

The median follow-up time was 28.1 months. Moreover, 188 out of 258 patients were ER-positive (72.9%), 154 (59.7%) patients were progesterone receptor (PR) positive, and 37.2% patients were HER2 positive. The median cut-off values for Ki67 index, ER, and PR were 32%, 55%, and 5%, respectively. The majority of the patients were categorized as luminal B (55.8%), luminal A (19.4%), triple-negative breast cancer (12.8%), and HER2-expressing type (12%) in the order of frequency. Table 1 shows the frequency of clinicopathological features of the patients.

TABLE 1: The clinicopathological features.

Characteristics	Number	%
Menopausal status		
Premenopause	160	62
Postmenopause	98	38
Tumor localization		
Right Breast	108	41.9
Left Breast	145	56.2
Bilateral	5	19
Clinical stage		
1	3	1.2
2	82	31.8
3	169	65.1
4	4	1.9
ER		
Positive	188	72.9
Negative	70	27.1
PR		
Positive	154	59.7
Negative	104	40.3
HER2		
Positive	96	37.2
Negative	162	62.8
Molecular Type	50	19.4
Luminal A	144	55.8
Luminal B	31	12
HER2 expressing triple negative	33	12.8
Grade		
Low	29	11.3
Intermediate	115	44.9
High	112	43.8
Operation type		
Breast-conserving surgery	66	25.6
Modified radical mastectomy	182	70.5
Simple mastectomy	10	3.9
Pathology		
Invasive ductal carcinoma	226	87.6
Invasive lobular carcinoma	13	5
Others	19	7.4
Tstage		
T0	58	22.5
T1	75	29.2
T2	81	31.4
T3	28	10.9
T4	16	6.2
Nstage		
N0	106	41.1
N1	69	26.7
N2	46	17.8
N3	32	12.4
X	5	1.9
Postoperative stage		
0	47	18.2
1	39	15.1
2	79	30.6
3	89	34.5
4	4	1.6
Lymphovascular Invasion		
Present	101	39.1
Absent	150	58.1
Unknown	7	2.7
Perineural Invasion		
Present	57	22.2
Absent	186	72.4
Unknown	14	5.4
Response to NAC		
CR	47	18.2
PR	134	5.9
PD	8	3.1
SD	69	26.7
Objective response rate		
PR-CR	181	70.2
PD-SD	77	29.3
Recurrence		
Present	58	22.6
Absent	199	77.4
Recurrence site bone	20	37
Local	9	16.7
Visceral	19	35.2
Brain	6	11.1

NAC: Neoadjuvant chemotherapy.

TABLE 2: The results of the overall survival (OS) and disease free survival (DFS).

Characteristics	5 year OS rate (%)	p	5 year DFS rate (%)	p
Operation type			67.1	0.01
Breast conserving surgery			59.3	
Modified radical mastectomy			20	
Simple mastectomy				
T stage			66	
T1			61.9	
T2			46.8	
T3			46.3	
T4			71.7	
T0				
Nstage	93	<0.001	73.4	<0.001
N0	93		66.7	
N1	84.5		44.5	
N2	69.5		41.3	
N3				
Postoperative stage	100	<0.001	73.8	<0.001
1	95.2		4.4	
2	78.6		40.3	
3	50		0	
4	100		73.2	
0				
Lymphovascular invasion			50.4	0.03
Present			63.5	
Absent				
Perineural invasion			40.1	0.003
Present			62.9	
Absent				
Response to NAC			73.2	<0.001
CR			69.4	
PR			0	
PD			42.4	
SD				
Postop stage				
0				
I				
II				
III				
IV				
NAC response categoric	89.9	0.03	70.2	<0.001
CR+PR	80.6		38	
SD+PD				
Recurrence	70	<0.001		
Present	100			
Absent				

NAC: Neoadjuvant chemotherapy,

The median DFS was 102 months (range: 31.7-173.5). The OS could not be reached at the time of analysis. Five-year OS and DFS were 88.5% and 59.2%, respectively. Although the surgery type (p=0.01), T stage (p=0.01), N stage (p<0.001), postoperative stage (p<0.001), LVI (p=0.03), PNI (p=0.003), and pathological response (p<0.001), were important for DFS, N stage (p<0.001), postop-

TABLE 3: The results of the chi-square test.

Characteristics	CR	PR	PD	SD	p
Menopausal status	33	91	2	34	0.02
Premenopause	14	42	6	35	
Postmenopause	0	-1	0	0	
Male					
ER	26	104	2	56	<0.001
Positive	21	30	6	13	
Negative					
PR	16	87	3	48	
Positive	31	47	5	21	<0.001
Negative					
Molecular classification	4	30	1	15	0.06
Luminal A	23	77	3	42	
Luminal B	10	13	2	5	
HER2 expressing	10	14	2	7	
Triple negative					
Hormone receptor	27	106	4	57	0.03
Positive	20	27	4	12	
Negative					
Lymphovascular invasion	9	41	8	43	<0.001
Present	37	88	0	25	
Absent	1	5	0	1	
Unknown					
Perineural invasion	1	19	5	32	<0.001
Present	42	107	3	34	
Absent	3	8	0	3	
Unknown					
Recurrence	5	21	5	27	<0.001
Present	42	112	3	42	
Absent					

NAC: Neoadjuvant chemotherapy, ER: Estrogen receptor, PR: Progesteron receptor, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

erative stage (p<0.001), objective response rate (p=0.03), and recurrence (p<0.001) were found to be prognostic indicators for OS by univariate analysis (Table 2).

The relation between pathological response and clinicopathological factors was evaluated using the chi-square test; the results are shown in Table 3. Menopausal status (p=0.02), ER (p<0.001), and PR (p<0.001), LVI (p<0.001), PNI (p<0.001), and recurrence (p<0.001) were associated with pathological response. Although CR was achieved more frequently in H-negative tumors than in H-positive counterparts (13.9% vs. 31.7%), SD was common among luminal tumors (29.3% vs. 19%). For all response types, recurrence was common among H-negative tumors. Objective response was achieved more frequently among tumors without LVI and PNI. ER (p=0.037, r=-0.130), PR (p=0.04, r=-0.177), and molecular type (p=0.04, r=-0125), and LVI (p<0.001, r=-0.326), PNI (p<0.001, r=-0.326) were negatively correlated with neoadjuvant response. In contrast, menopausal status (p=0.004) and clinical stage (p=0.03, r=0.184) were positively correlated with the response by Spearman's test (Table 4).

DISCUSSION

NAC is increasingly being used in patients with operable breast cancer to allow more limited surgery for both breast and axillary lymph nodes by shrinking the tumor or increasing the resectability for locally ad-

TABLE 4: The results of correlation analysis.

Characteristics	ORR p	ORR r
Menopausal status	0.004	0.177
Clinical stage	0.003	0.184
Postoperative stage	0.001	-0,211
T stage	<0.001	-0,545
Nstage	<0.001	0.704
Clinical stage	0.04	0.174
PR	0.04	-0,177
ER	0.037	-0,130
Molecular type	0.04	-0,125
Grade	0,9	0.001
Recurrence	<0.001	0.704
Lymphovascular invasion	<0.001	-0,326
Perineural invasion	<0,001	-0,354

N AC: Neoadjuvant chemotherapy, ER: Estrogen receptor, PR: Progesteron receptor, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

vanced tumors.[11] Clinical and pathological responses are important factors for recurrence and survival after NAC.[6] PCR ranged from 33 to 37% for breast and 40 to 49% for axillary lymph nodes with chemotherapy, including anthracycline with/without taxane.[6,12,13] For H-positive tumors, 13% PCR was achieved; PCR has been reported as a better outcome irrespective of the H status.[14]

PCR after NAC correlated with tumor subtypes.[1] PCR is achieved in a minority of ER-positive tumors (range: 2-10%).[15] We achieved 13.9% of PCR among hormone-positive tumors with a slightly higher than that reported in the literature. It could be related to the degree of positivity of H. The literature cites the response to NAC among breast cancer molecular subtypes; one of them was in the Russian population. Among the 231 patients, nearly half of them were H-positive (48.9%), and PCR was 4.5%, which was lower than that reported in our population (1/3 and 18.2%, respectively).[16] The difference could be related to the schedule of the treatment and prevalence of the subtypes in different populations. In the literature, ER and PR expression was categorized as ≥50%, and 0 to 49% among 533 luminal type breast cancer, and PCR could not be reached in the first group. However, the rate of PCR was 3.3% among the second group.[17] In one meta-analysis, the PCR for both breast and axilla was the highest for triple-negative (27.5%) and HER2-positive (26.5%) than H-positive tumors (7.2%).[1] The PCR was 46.4% using the HER2-directed therapy for HER2-positive tumor.[1] Moreover, one of the proliferation index parameters, Ki67% was reported to be a predictive marker for NAC.[18] Similarly, we found statistically significant differences among PCR with respect to luminal A and B tumors (8.5% vs. 48.9%, $p<0.05$).

Hirata's study described age, clinical stage, grade, HER2 status, clinical response, and the number of lymph node metastasis as important factors for DFS.[4] Furthermore, we found surgery type, T and N stages, postoperative stage, LVI, PNI, and treatment response to be associated with DFS. Postoperative stage, N stage, treatment response, and recurrence were important for OS. Minckwitz et al. demonstrated that PCR to NAC was not prognostic for luminal A tumors We could not find molecular subtypes as an important prognostic factor for survival, as reported in the literature.[8,16] However, the pathological response was significant for both OS and DFS.

Gentile et al. reported that 25% PCR correlated with tumor biology but not with the extent of the tumor after NAC for 321 patients with LABC.[13] In their study, 43% of patients had H-positive tumors different from those reported in our study. Over two-thirds of our patients had H-positive tumors, indicating that different race affected the tumor subtype. PCR was significantly more common in the axillary lymph node than in the breast tissue, a finding similar to our study. Differently, we found that the pathological response correlated with both tumor extent (T and N stages) and molecular subtype. PCR was higher in H-negative groups than in the positive ones (31% vs. 13.9%, $p = 0.001$).

The intrinsic subtype of breast cancer did not completely overlap with pathology-based biomarkers such as ER, PR, Ki67, and HER2 determined by immunohistochemical analysis.[19,20] Intrinsic subtypes of breast cancer (PAM50) was determined by gene expression profiling. The risk of relapse score (ROR) was reported to be associated with PCR, independent from clinicopathological variables.[21] In the neoadjuvant-treated and clinically node-negative patients with low ROR score, the 5-year distant relapse-free survival was 97.5%.[21] The absolute benefit of cytotoxic chemotherapy for luminal A tumors, according to gene profiling, is small.[21] Although PCR was lower in the luminal group (6% for

luminal A and 16% for luminal B tumors, as detected by PAM50), it did not show ER or PR as an independent predictive marker for a response when intrinsic subtypes were introduced into the mode. Moreover, MammaPrint was compared with conventional clinical subtypes determined by IHC with respect to the response to NAC.[22] Although PCR for patients with luminal tumor subjected to NAC was 11%, it was 32% after the BluePrint test because 18% of the patients are reclassified into different groups after this test.[2] In our study, PCR was 8.5% for luminal A and 48.9% for luminal B tumors, which was determined by IHC, and hormone positivity was related to the pathological response by chi-square test and correlation analysis, respectively. However, we do not know if intrinsic subtypes were included in the study. PAM50 score would not be possible routinely for the majority of the patients in our country as its cost is not covered by social insurance. Our results were noteworthy because these not only supported the low PCR for luminal tumors, especially for luminal A tumors but also showed clinical importance of response rate both in DFS and OS among the Turkish population.

CONCLUSION

Breast cancer is a heterogeneous disease with no single treatment plan for all types. It would be better if NAC is used for patients with breast cancer with low hormone positivity and high Ki67 values. If a low risk for recurrence is determined clinicopathologically before NAC, the patient and physician can weigh the risk and benefit ratio and the patient can be operated on without exposure to toxic effects of chemotherapy.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bala Başak Öven;* ***Design:*** *Serkan Çelik;* ***Control/Supervision:*** *Günay Gürleyik;* ***Data Collection and/or Processing:*** *Fügen Aker Vardar, Bala Başak Öven;* ***Analysis and/or Interpretation:*** *Mesut Şeker, Serdar Çelik;* ***Literature Review:*** *İlker Nihat Ökten, Serkan Çelik;* ***Writing the Article:*** *Ezgi Yüzügüllü;* ***Critical Review:*** *Ali Aktekin;* ***Materials:*** *Fügen Aker Vardar.*

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